REVIEW ARTICLE

Usefulness of Positron Emission Tomography–Computed Tomography in Respiratory Medicine

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The introduction of positron emission tomography (PET) into the management of neoplastic disease in respiratory patients signified an important change from classic algorithms based exclusively on anatomic information obtained through computed tomography (CT).

Non-small cell lung cancer and solitary pulmonary nodule were the 2 diseases in which metabolic PET imaging offered the highest diagnostic yield, as has been evident since the inclusion of this technology among the services available within the Spanish national health service. However, a number of limitations were encountered in relation to the lack of anatomic definition in PET imaging, as had been described in the literature.

The appearance in 2001 of hybrid PET-CT devices has not only helped remedy those defects, but has also made it possible to combine anatomic and metabolic information in a single image, making this hybrid technology the most valuable tool in the current diagnostic arsenal.

Key words: *Fluorodeoxyglucose-positron emission tomography (FDG-PET). Positron emission tomography–computed tomography (PET-CT). Lung cancer. Solitary pulmonary nodule.*

Utilidad de la tomografía por emisión de positrones-tomografía computarizada (PET-TC) en neumología

La introducción de la tomografía por emisión de positrones (PET) en el manejo del paciente con enfermedad neoplásica en neumología supuso un importante cambio respecto a los algoritmos clásicamente basados sólo en la anatomía que ofrecía la tomografía computarizada (TC).

El carcinoma pulmonar no microcítico y el nódulo pulmonar solitario fueron las 2 enfermedades donde mayor rendimiento diagnóstico ofreció la imagen metabólica PET, como ha quedado demostrado tras su reciente incorporación a la cartera de servicios comunes del Sistema Nacional de Salud. Sin embargo, la falta de delimitación anatómica de la imagen PET conllevaba una serie de limitaciones que habían sido descritas en la literatura médica.

La aparición de los equipos híbridos PET-TC en 2001 ayudó no sólo a corregir estos defectos, sino que además, al unir la información anatómica y metabólica en una sola imagen, ha hecho que esta tecnología sea la más valiosa dentro del arsenal diagnóstico actual.

Palabras claves: *Tomografía por emisión de positrones-fluoro-2-desoxi-D-glucosa (PET-FDG). Tomografía por emisión de positrones-Tomografía computarizada (PET-TC). Cáncer de pulmón. Nódulo pulmonar.*

Introduction

Since the introduction of integrated positron emission tomography–computed tomography (PET-CT) into clinical practice by the University of Zurich group in 2001, these scans combining the anatomic image obtained by CT and the metabolic image produced by PET—made possible by new hybrid scanners and fusion stations—have brought about a veritable revolution in diagnostic imaging, especially in cancer patients.[1] PET-CT imaging has made it possible to combine 2 complementary specialties—nuclear medicine (PET) and radiography (CT)—thereby achieving an objective long desired in the field of diagnostics. The resulting hybrid scanner is a diagnostic tool that increases the efficacy of the metabolic technique by combining anatomic and metabolic data in a single image, an advance that reduces by 20% to 30% the false positive and negative results traditionally associated with the use of PET in oncology.[2] The object of the combination, in short, is to achieve a better diagnostic yield than that obtained using the 2 techniques separately, thereby improving management of neoplastic disease and consequently survival rates.

Recent reports on the clinical value of this new imaging technique published by the agencies that evaluate health

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technologies have served to heighten the interest that had already been generated in the medical world.[3,4] Nine Spanish autonomous communities have PET-CT scanners, and current plans are to increase this to 11 by the end of 2007. Since 2 years ago, all new imaging equipment purchased and replacements for existing PET scanners have been PET-CT scanners or workstations capable of merging PET images with data from either CT or magnetic resonance imaging (MRI) equipment. The team of researchers at the University of Tennessee that developed the first PET-CT camera in 1998 is now working on a new hybrid PET-MRI scanner, which in time will be another advance in diagnostic imaging. As PET-CT has existed for barely 5 years, larger studies are needed to confirm whether the diagnostic yield of this technique is better than that obtained using the component technologies performed separately. However, the literature is now beginning to confirm the important diagnostic advantages of PET-CT in cancer patients,[5] especially when it is used all-inclusively (diagnostic CT, diagnostic PET, and combined imaging) rather than partially (non-diagnostic CT for anatomic localization and diagnostic PET).

The radiopharmaceutical most commonly used for PET imaging in clinical practice is 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG). Since this is the only metabolic tracer for PET approved by the Spanish Ministry of Health and Consumer Affairs, we will focus exclusively on it rather than on thymidine or choline, which have both also been used in respiratory disease. Furthermore, as ^{18}F-FDG is an excellent tracer for detecting tumor metabolism, our focus in this review will be on the malignant neoplastic respiratory diseases, in particular non-small cell lung cancer (NSCLC) (Table 1). In fact, the indications for PET-CT in the field of respiratory medicine contemplated by the Spanish public health authorities are NSCLC staging and the study of solitary pulmonary nodules.

Characterization of Solitary Pulmonary Nodule

A solitary pulmonary nodule is defined as a dense round- or oval-shaped radiographic lesion under 3 cm in diameter totally surrounded by normal lung tissue; lesions with a diameter larger than 3 cm are called masses and are generally malignant.

The discovery of a solitary pulmonary nodule on plain chest radiography or CT is a common occurrence, and such nodules are the most common manifestation of lung cancer in asymptomatic patients. However, since only 40% of these lesions are malignant, a careful selection process is needed to identify patients requiring surgery. Although several clinical and radiographic criteria have been proposed for differentiating between benign and malignant solitary pulmonary nodules, most such lesions are classified as indeterminate.

Some hospitals use dynamic helical CT to study solitary pulmonary nodules, evaluating possible enhanced uptake of iodinated contrast in the nodule by measuring increased density as expressed in Hounsfield units (HU). Using a cutoff value of 15 HU, this technique achieves very high levels of sensitivity for the diagnosis of malignancy (almost 100%); however, the same criterion provides only mediocre specificity. Consequently, the value of this test lies in its high negative predictive value as it can rule out malignancy with certainty in cases where no enhancement is observed. Although dynamic MRI performed with paramagnetic contrast media has also been used for this purpose, the initial results indicate that yield is similar to that obtained with dynamic CT. Various other procedures that fall outside the area of diagnostic imaging have also been used to establish a differential diagnosis for solitary pulmonary nodule. These include sputum cytology, fiberoptic bronchoscopy, fine needle aspiration, and video-assisted thoracoscopy.

PET measures FDG uptake in the nodule, a noninvasive parameter that facilitates the characterization of solitary pulmonary nodules. Uptake correlates with both the size of the nodule and its metabolic activity, both aspects that contribute to the creation of a sufficiently high signal-to-background contrast to facilitate detection of the nodule. Size is conditioned by the resolution of the scanner, which varies between 6 and 10 mm. Metabolic activity (and consequently FDG uptake) depends on the vascularization of the nodule, the rate of cell glycolysis, and the expression of glucose transporter molecules and intracellular phosphorylation enzymes. Hypermetabolic nodules with high FDG uptake showing greater activity than the surrounding mediastinal tissue are considered malignant and those with little or no activity are considered benign. In a classic meta-analysis carried out by the Stanford University group,[6] FDG was found to have a sensitivity of 96.8% and a specificity of 77.8% for the identification of malignancy. Although the sensitivity and specificity values reported in many published series differ from these results, there is consensus on the safety of the technique, which has been shown to be around 90%. PET-CT is now being used to study solitary pulmonary nodules,[7] and this is one of the indications for PET currently being scrutinized and evaluated by the Spanish Ministry of Health and Consumer Affairs. The results of their research have recently been published (Figure 1).[8]

Correct evaluation of solitary pulmonary nodule using FDG requires an understanding of the mechanisms of false positives and the reasons for glucose uptake in nonproliferative nodules. Causes of false positives include the presence of inflammatory and infectious diseases (tuberculosis, histoplasmosis, sarcoidosis, aspergillosis), pulmonary embolism, and test-related artifacts. It is also important to be aware of the reasons why certain tumoral nodules may evidence scant uptake and give rise to a false negative interpretation.[9] The most common causes of false

TABLE 1
Indications for Positron Emission Tomography–Computed Tomography in Respiratory Medicine*

Characterization of solitary pulmonary nodule
Mediastinal and extrathoracic staging of NSCLC
Assessment of treatment response in NSCLC
Follow-up, detection of recurrence, and prognostic value in NSCLC
Radiation therapy planning
Detection of malignant pleural disease

*NSCLC indicates non-small cell lung cancer.

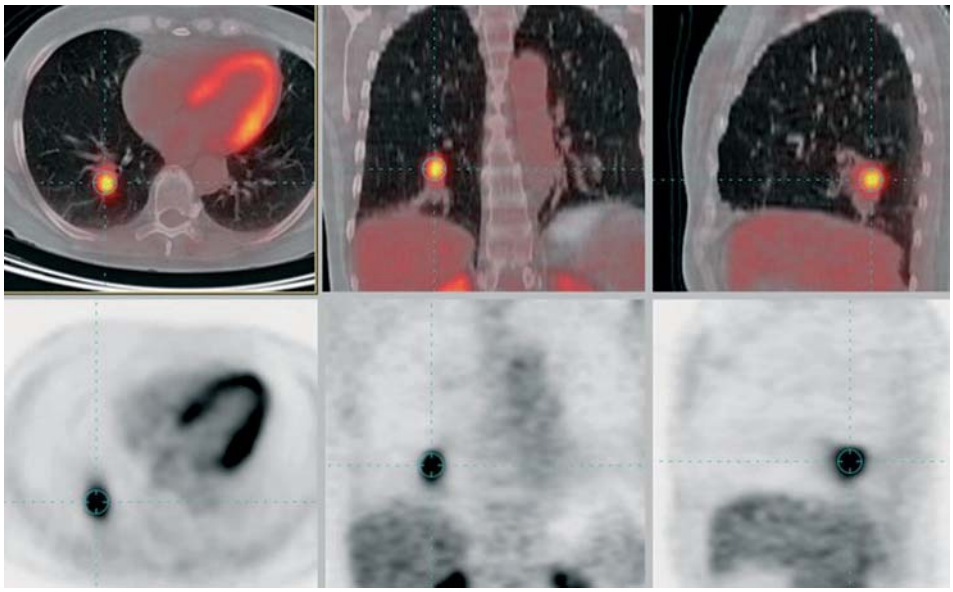

Figure 1. Characterization of a right lung nodule of unknown etiology. Positron emission tomography–computed tomography: nodular lesion suggestive of a tumor in segment 10, right.

negatives are small lesion size (the lower limit of scanner resolution is between 6 mm and 10 mm) and low grade malignancy (bronchioloalveolar and mucinous carcinomas and carcinoid tumors).

Joint evaluation of radiographic signs and late measures of the standardized uptake value (SUV), 2 to 3 hours after tracer injection, can help to rule out some of the potential causes for false positives and negatives.[10] A CT pattern indicative of granulomatous disease will facilitate correct interpretation of a hypermetabolic nodule. Furthermore, as FDG uptake usually increases over time in malignant lesions, a late scan (2 to 3 hours after FDG administration) is recommended in doubtful cases. Conversely, in benign lesions FDG uptake tends to remain stable or decrease in later scans.

Occasionally, FDG images show artifacts in the form of hypermetabolic nodules for which no matching evidence is found on CT scans. These artifacts are generally caused by the presence of microembolisms associated with endothelial damage caused by extravasation of the radiopharmaceutical.[11] When there is doubt about the diagnosis, the scan should be repeated some days later to ensure that the nodule has disappeared.

False negatives are caused by the existence of low grade, slow growing tumors or subcentimeter nodules that fall below the lower limit of resolution for the PET scanner. The SUV may be underestimated in small lesions (<2 times the spatial resolution of the scanner), and diagnostic certainty can be improved by correction of the SUV based on the actual size of the nodule as measured by CT. However, it should be remembered that the prevalence of malignancy in small nodules is low. Moreover, the existence of a visible nodule on CT with a pattern indicative of bronchioloalveolar carcinoma or a carcinoid tumor will help to reduce potential false negative interpretations based on PET images alone. Respiratory motion has also recently been shown to hinder the detection of pulmonary nodules by PET, in particular those located near the base of the lungs; dispersion of the image across the trajectory of the movement leads to a marked reduction in uptake. By synchronizing data acquisition with the respiratory cycle (gating) or applying various respiratory protocols, visible uptake (SUV) can be increased to facilitate detection and characterization of the lesion.[12,13]

FDG uptake correlates closely with tumor growth and proliferative capacity. Using multivariate analysis, many authors have shown SUV to be a prognostic factor that provides information concerning the evolution of disease in these patients independent of clinical stage and lesion size. The highest SUVs (≥7) are associated with the highest grade tumors and, consequently, the worst prognosis. These higher values are probably the result of the more aggressive biological behavior of these lesions.

In view of the high negative predictive value of PET-CT, no further tests are required when a solitary pulmonary nodule is classified as benign on the basis of this imaging technology (Table 2). However, when a nodule is classified as malignant, diagnosis should be confirmed by invasive methods. When there is a discrepancy between morphological and functional information, the action that should be taken will vary depending on each situation. When a nodule is found with scant or no metabolic activity but the radiographic signs suggest malignancy, needle biopsy or surgery should be performed. However, when the morphological criteria indicate a benign lesion but the nodule is hypermetabolic, the tumor should be treated as malignant. An exception to this rule is a hypermetabolic lesion associated with a morphological picture indicative of granulomatous disease or pneumonia. Occasionally, a hypermetabolic nodule observed on PET is not matched by any CT finding. This is usually an artifact of the image fusion process caused by respiratory motion, and the nodule should be found in nearby axial slices in a cranial or caudal direction. In the case of subcentimeter nodules, which

may fall below the lower limit for detection by PET and therefore be difficult to characterize metabolically, a repeat scan should be performed at 3 months. In such cases the volume and metabolic activity of the nodule should be assessed, and if any increase is found in either of these parameters, the nodule should be treated as malignant.

Non-Small Cell Lung Cancer

Mediastinal and Extrathoracic Staging

The radical treatments used to treat NSCLC are surgery—if criteria for resectability are fulfilled—and radiation therapy. Resectability depends on staging, location, and the size and extent of the tumor. The TNM classification system is the tool most widely used for this purpose. In this system, the T refers to the size and site of the primary tumor and any invasion of adjacent structures; the N refers to spread to lymph nodes; and the M to the presence or absence of distant metastasis. There is general agreement that tumors up to stage IIB are resectable, while stage IIIB and IV tumors are not. The difficulty arises with stage IIIA tumors, for which the literature recommends surgery complemented by adjuvant chemotherapy or neoadjuvant chemotherapy followed by surgery. When surgery is precluded by medical contraindications, radical radiation therapy is an alternative treatment option. The primary aim of imaging studies is to identify patients suitable for surgery or curative radiation therapy. In this context, correct evaluation of the mediastinum is crucial and the possible existence of metastasis must be ruled out.

The T factor can be accurately assessed on the basis of the morphological data provided by CT scans and sometimes by MRI. However, there are 4 situations in which the hybrid metabolic-morphological images produced by PET-CT can play a key role in correct assessment of the tumor: *a*) when there is collapsed or consolidated lung distal to the tumor; *b*) assessment of satellite nodules; *c*) evaluation of possible pleural involvement; and *d*) selection of the most appropriate sampling sites. The metabolic information makes it possible to visualize the tumoral mass and differentiate it from areas of collapsed lung (atelectasis) and areas of infectious or inflammatory activity around the tumor (pneumonitis). The metabolic activity matching the radiographic pattern in peritumoral pneumonitis is weaker and more diffuse than the more focal and intense activity of the tumor itself. A central hypermetabolic tumor is usually visible in atelectasis together with partial occlusion of the bronchial tree, a phenomenon that gives rise to an area of collapsed lung with no significant metabolic activity. The criterion for evaluating satellite nodules is similar to that described for solitary pulmonary nodule. Detection of multiple hypermetabolic nodules in a single lobe classifies the tumor as T4, but these nodules are not considered to be metastases. Pleural involvement is relatively common in patients with lung cancer. Differentiating between malignant and benign tumors is an essential step in the process of identifying cases suitable for resection and radiotherapy. Although pleural nodularity, thickening, and uptake are all indications of infiltration, both CT and MRI have limitations when it comes to providing definitive answers in this context. However, it should be noted that the proportion of false negatives after thoracentesis, an invasive procedure, is 30% to 40%. Evidence of metabolic activity and/or nodularity in the thickened pleura is suggestive of malignancy. In patients who have undergone talc pleurodesis, findings should be evaluated carefully because the presence of intense accumulations of FDG may lead to false positive results; the presence on the CT scan of pleural thickening accompanied by an increase in attenuation will help to clarify the result. In any event, a positive result should be confirmed by other tests. In view of the high negative predictive value of functional imaging, the number of invasive procedures can be reduced when the metabolic findings indicate a benign pleural effusion.

TABLE 2
Recommendations for the Management of Solitary Pulmonary Nodule Based on Information From Positron Emission Tomography (PET)–Computed Tomography (CT) Imaging*

PET Finding	CT Finding	Recommendation
FDG–	Benign	High probability of a benign process: monitor
FDG+	Malignant	High probability of malignancy
FDG–	Malignant	High probability of malignancy
FDG+	Benign	Confirmation of PET findings
FDG+	Infection/ inflammation	High probability of a benign process: confirmation of PET finding
FDG+	No evidence of any lesion	Artifact of movement/ microembolism after injection
FDG–	Subcentimeter nodules	Monitor

*FDG indicates fluorodeoxyglucose.

Finally, samples should be taken from the sites where the most intense metabolic activity is detected, and particular care should be taken to exclude ametabolic areas (which correspond to intratumoral necrosis).

It is well known that metastatic spread to mediastinal lymph nodes is a factor limiting surgery in NSCLC (squamous cell carcinoma, adenocarcinoma, and large cell carcinoma). It is, therefore, of key importance to obtain the most accurate staging possible of the mediastinal lymph nodes before any decision is taken regarding radical treatment. Patients with contralateral mediastinal lymph node metastasis (N3) or advanced N2 stage disease (technically unresectable large ipsilateral nodes) will not benefit from radical surgery. CT provides only presumptive evidence of metastatic disease in the mediastinum, and this is not sufficient to support a therapeutic decision. In many patients, tumoral stage is underestimated or overestimated when staging is based solely on CT findings. The fact that node involvement is found in approximately 26% of patients at the time of diagnosis justifies the

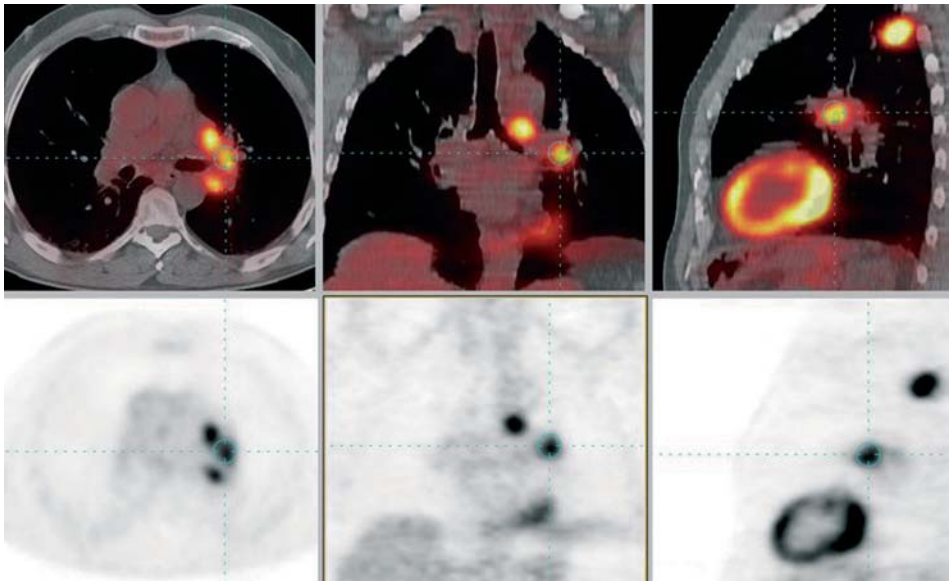

Figure 2. Mediastinal staging of non-small cell lung cancer. Positron emission tomography–computed tomography: malignant lesion in the upper left lobe with enlarged nodes in the aortopulmonary window and the left pulmonary hilum.

performance of a staging mediastinoscopy before any therapeutic decision is made. There is a growing body of literature on the value of FDG-PET in lung cancer staging.[14,15] Interest is due to the proven value of this technique for accurately diagnosing the spread of disease both inside and outside the chest and for providing the information needed to guide the selection of appropriate treatment in each clinical situation. It should be remembered that in a single test FDG-PET can assess the extent of disease both inside and outside the chest and identify cases not suitable for surgery owing to the presence of occult distant metastasis. Although FDG uptake in the primary tumor does not predict prognosis in patients with NSCLC, staging based on PET findings in these patients stratifies survival without disease with greater certainty than staging with CT.[16] In a study published by Pieterman et al,[17] the sensitivity and specificity of PET in the evaluation of mediastinal lymph nodes in these patients were found to be 91% and 86%, respectively; in the same study, CT imaging had a sensitivity of 75% and a specificity of 66%. In an earlier meta-analysis of 514 patients studied with PET and 2226 patients studied using CT, the authors found a sensitivity and specificity for detection of mediastinal metastases in this clinical context of 79% and 91%, respectively, for PET, while for CT these figures were 60% and 77%, respectively.[18] It is not unusual to find significant FDG uptake in mediastinal lymph nodes unrelated to any metastatic lesion. However, the positive predictive value of PET in the mediastinum is 70%. PET improves the detection rate for both local and distant metastases in patients with NSCLC.[19] It is a powerful noninvasive diagnostic imaging test capable of detecting metabolic alterations in cells, and it provides a higher degree of certainty in staging this type of cancer than do other methods. The cost of PET is compensated by the reduction in the number of surgical procedures required in patients with mediastinal neoplastic disease or systemic metastatic dissemination, and this cost-effectiveness has been demonstrated.[20]

PET-CT increases diagnostic certainty by facilitating the detection of granulomatous disease on the basis of morphological information provided by the CT component or by ruling out a positive result in the case of marginal accumulations in vascular structures. It also facilitates correct assessment of small nodes (in which the SUV can be underestimated) and accurate anatomic localization of the hypermetabolic foci (Figure 2). Correlation of PET and CT data also makes it possible to rule out a pathologic cause in the case of FDG accumulation in supraclavicular brown fat (a result of dopaminergic activation) or neck muscle. In a recent retrospective study, the University of Leuven group[21] reported better TNM staging with PET-CT (80%, 98%, and 70%, respectively) than with CT alone (66%, 88%, and 46%, respectively), or PET after visual correlation with CT (68%, 96%, and 54%, respectively).

Mediastinoscopy is the instrumental technique most widely used to confirm PET-CT findings. Although this procedure has limitations for the assessment of some node stations (aortopulmonary window, anterior mediastinum), it is currently considered to be the procedure of choice for confirming node involvement. It has a sensitivity of approximately 90%. Because false positives are possible with PET-CT, a positive result must be confirmed by mediastinoscopy using the scanned image as a guide. However, in view of the high negative predictive value of PET-CT, mediastinoscopy is not necessary when hybrid imaging reveals no evidence of mediastinal lymph node involvement.

Evidence of metastatic disease at the time of diagnosis is a fairly common finding that precludes curative treatment. Other patients develop metastasis after treatment, probably an indication that micrometastatic spread was already present at the time of diagnosis. It is, therefore, of crucial importance that a thorough assessment be undertaken to

evaluate the possibility of extrathoracic involvement. PET has been shown to have a better diagnostic yield than CT in the study of metastasis. The integration of functional data with the anatomic information provided by CT has led to changes in the clinical management of a significant number of patients (10%-40%).

As PET-CT is performed using a whole body scanner that integrates the morphological and functional data acquired by each technique, it is an ideal tool for studying metastatic disease (Figure 3). A typical scan covers the area from the base of the brain down to the upper section of the lower limbs including (with some exceptions, such as the brain) all the locations where metastases most often occur in NSCLC (adrenal glands, bone, liver, lungs, soft tissue). Enlarged adrenal glands (incidentalomas) are quite often found on the CT scans of patients with NSCLC (10%-15%). However, a third of these tumors are benign. As the information provided by the PET scan has a high yield for confirming or ruling out metastases, it reduces the number of biopsies that must be performed. When a hypermetabolic adrenal nodule is found, the existence of metastasis should be confirmed by needle aspiration biopsy. In the case of subcentimeter nodules only visible on CT scans (an exceptional situation), the possibility of a false negative must be considered. With respect to bone metastases, the data provided by the PET-CT scan has a similar sensitivity (90%) to bone scintigraphy but a higher specificity (>98% as compared to 60%). Lower metabolic activity has been reported in osteoblastic metastases, but mainly in the context of other tumors, such as breast and prostate cancer. Owing to the low number of false positive results it produces and the fact that it can detect soft tissue involvement, PET-CT is considered to afford an excellent yield in the study of this type of metastasis, with some authors reporting diagnostic accuracy of over 96%.[22]

PET-CT is also a useful exploratory tool for the detection of liver metastasis. The information provided by the PET component adds value to the CT data, reducing the number of false positive results and confirming tentative findings. Subcentimeter metastases can, however, give rise to false negatives. The procedure for evaluating pulmonary metastases in patients with NSCLC is the same as that described above for solitary pulmonary nodule. Lymphangitic carcinomatosis should be suspected if CT reveals a reticulonodular pattern with thickening of the septal lines showing a diffuse increase in FDG uptake. Using PET-CT, it is sometimes possible to visualize a synchronous tumor, particularly one located in the colorectal region. However, this hybrid imaging technique is not very useful for detecting and evaluating the possibility of cerebral metastasis, and MRI is the procedure of choice when brain involvement is suspected. The spatial resolution of PET imaging is limited, and the intense physiological uptake of FDG in the cortical regions obscures the presence of pathologic uptake indicating metastasis. Although evidence of metastasis normally takes the form of a

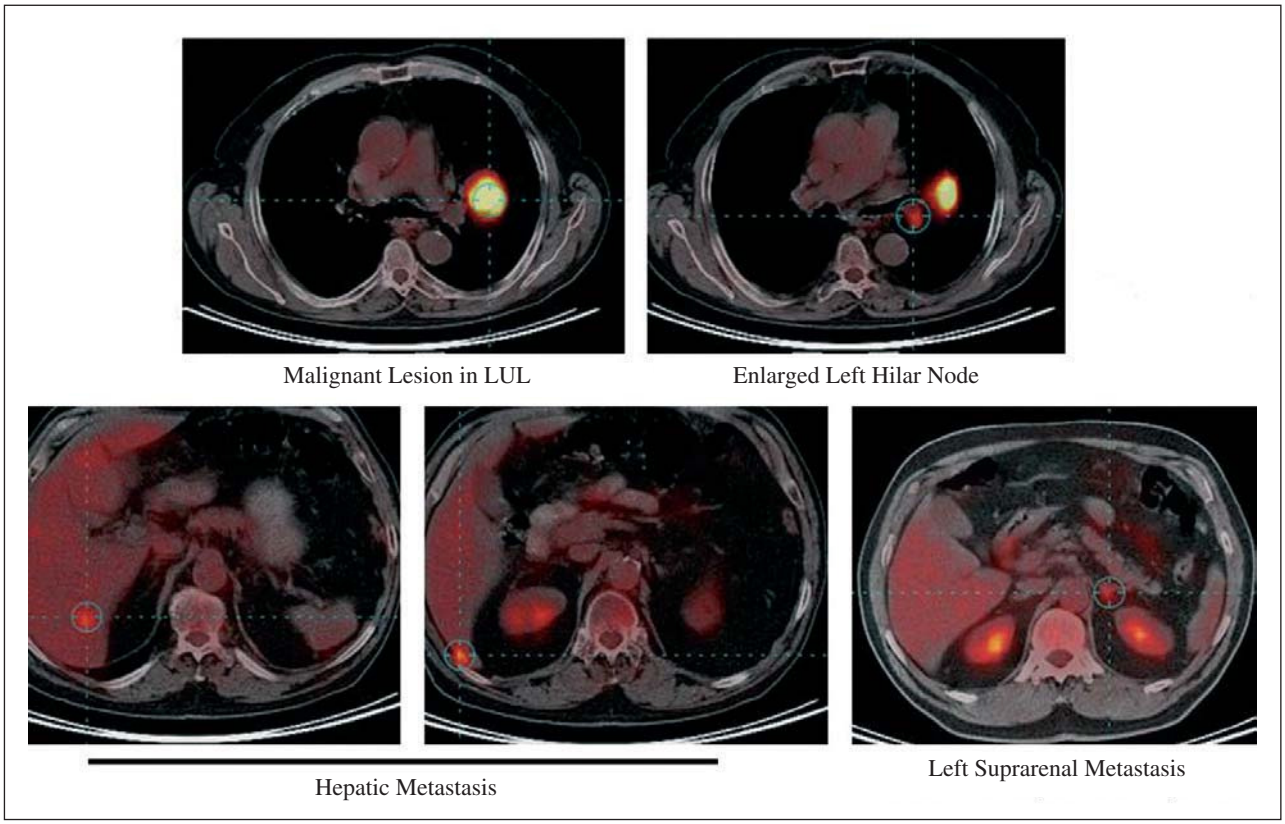

Figure 3. Mediastinal and extrathoracic staging of non-small cell lung carcinoma. LUL indicates left upper lobe.

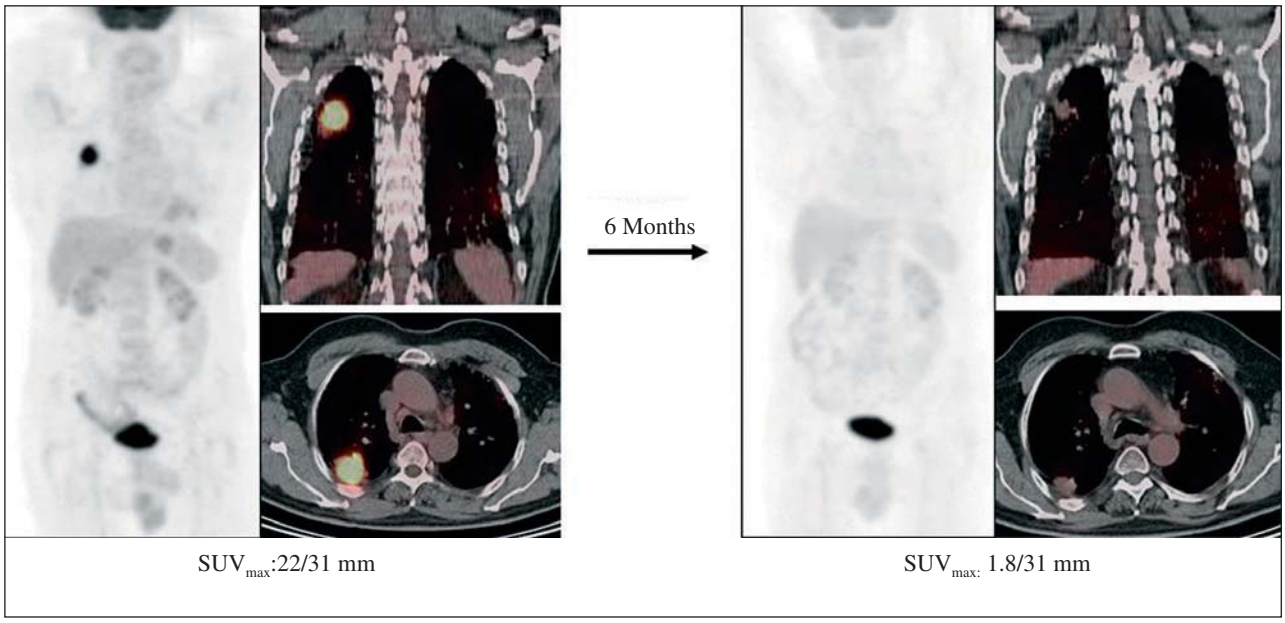

Figure 4. Evaluation of response to chemotherapy and radiotherapy in non-small cell lung cancer located in the upper right lobe. Positron emission tomography–computed tomography: reduction in size and marked decrease in metabolic activity of a neoplastic lesion in segment 2 of the right lung. SUV_{max} indicates maximum standard uptake values.

hypermetabolic focus, the metabolic pattern can vary considerably. An increase in FDG uptake is sometimes seen in a vocal chord when the recurrent laryngeal nerve is affected by the tumor or the enlarged nodes. This leads to overuse of the healthy vocal chord (physiologic compensation)—which causes the increased uptake—and paralysis of the affected chord. PET-CT scanning has reduced the number of false positives from PET, primarily by making it possible to exclude the metabolic activity in muscles and brown fat as a source of error.

Staging in patients with NSCLC is one of the indications for PET that was recently evaluated by the Spanish Ministry of Health and Consumer Affairs, and the results of this research have been published.[8]

Assessment of Therapeutic Response

When imaging is used to assess response to treatment, the results of a post-treatment study are compared to those of a baseline study. A morphological parameter is currently used to determine response to treatment: the reduction in tumor size as measured by CT. A set of rules called the response evaluation criteria in solid tumors (RECIST) is used to make this assessment. Disease is evaluated by measuring the longest diameter in the axial plane of each of the target tumor masses, and total tumor size is defined as the sum of the diameters measured. This criterion is used to define 4 outcomes: complete response (disappearance of tumor), partial response (a reduction of at least 30% in tumor size), stable disease (no change), and progressive disease (an increase in tumor size of at least 20%).

The functional data provided by the PET scan define a view unrelated to size, which is therefore free from the errors caused by the inherent difficulty of differentiating between fibrosis and tumor on the basis of a morphological assessment. Metabolic data from the PET scan provides information about the increase, persistence, reduction, or disappearance of FDG uptake by the tumor. Prognosis is good when metabolic activity in the tumor has completely disappeared and poor when such activity persists after treatment. The only limitation of PET in this context is its insensitivity to microscopic disease when the volume of lesions is below the lower limit of resolution of the scanner.

The European Organisation for Research and Treatment of Cancer defines a reduction of between 15% and 25% in the SUV after a cycle of treatment as a partial metabolic response. However, larger studies and meta-analyses are needed to define with greater rigor the criteria for assessing response after courses of chemotherapy, particularly for use with PET-CT because it combines anatomic and metabolic data.

The value of PET in the assessment of response to chemotherapy has been reported by various authors of prospective studies. For example, in a pilot study, Vansteenkiste and colleagues[23] found that PET was more useful than CT in the assessment of tumor downstaging and had predictive value: prognosis was better in patients in whom PET provided evidence of response (defined as mediastinal clearance and a decrease of at least 50% in the SUV of the primary tumor) than in those with no response.

Some authors have even suggested that PET could be a valid tool for selecting cases suitable for intensive local-regional treatment after induction chemotherapy.[24] Ryu et al[25] found PET to have high sensitivity (88%) but limited specificity (67%) for detecting residual

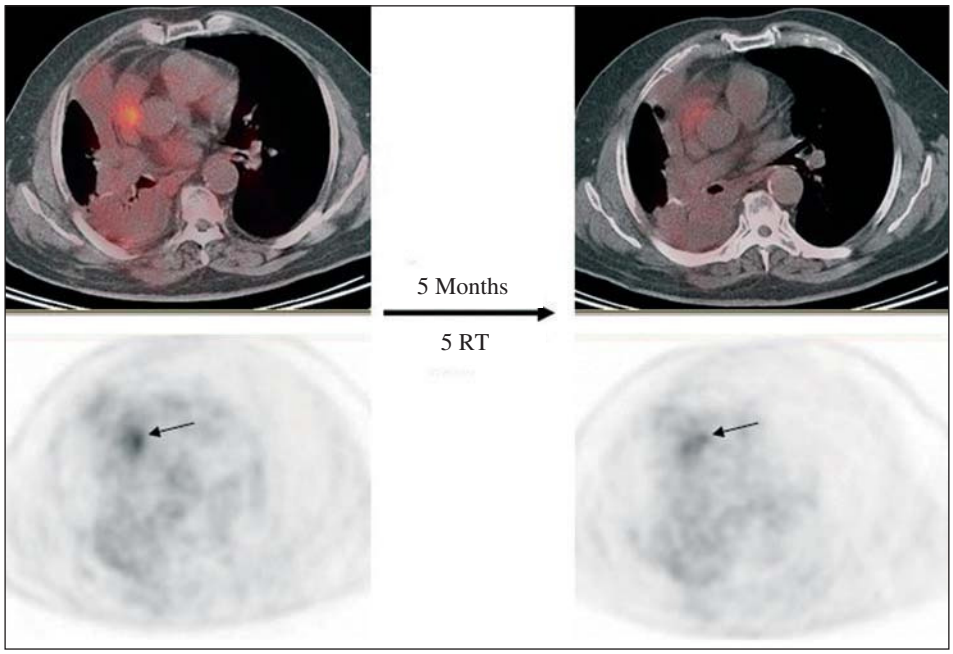

Figure 5. Epidermoid lung carcinoma T4 N0 M0. Neoadjuvant chemotherapy. Evaluation of residual activity after radiotherapy (RT). Possibility of rescue surgery. Positron emission tomography–computed tomography: fluorodeoxyglucose uptake after RT showing post-treatment changes.

disease in the primary tumor but, by contrast, high specificity (93%) and limited sensitivity (58%) for restaging mediastinal nodal lesions. Akhurst et al[26] showed how PET overstaged nodal tumor status in 33% of patients and understaged it in 15% after induction therapy (principally chemotherapy). Pottgen et al[27] described the value of PET-CT in predicting response after neoadjuvant chemoradiotherapy in 55 patients. These authors point out the value of this imaging technique not only for the selection of patients suitable for surgical resection but also for predicting response to treatment in both the primary tumor and mediastinal lymph nodes.

At any rate, only limited evidence is available[28] and larger studies are needed before current anatomic criteria for treatment response (RECIST) can be modified, especially in small-cell lung cancer.[29]

Follow-Up, Detection of Recurrence, and Prognostic Value

In patients in whom recurrence or changes are suspected following treatment, PET has been reported to have a sensitivity of between 97% and 100%, a specificity of between 62% and 100%, and a diagnostic precision of between 78% and 98%.[30] Performing PET scans shortly after completion of radiotherapy may give rise to false positive results caused by radiation pneumonitis or the presence of macrophages in tumor necrosis.[31,32] Pneumonitis is common after radiation therapy, with a peak occurring between 6 and 12 weeks after completion of treatment. To obtain an accurate evaluation of tumor viability, an interval of 4 to 6 months is recommended between completion of radiotherapy and the post-treatment PET scan (Figure 5).

PET is an imaging technique with important anatomic limitations which can often make it difficult to localize the detected lesion. In the case of recurrent disease, the combination of an anatomic picture altered by treatment and FDG uptake in zones affected by post-treatment inflammation may interfere with the correct interpretation of metabolic studies.[33] This problem is to a large degree resolved by the new integrated PET-CT scanners.[34]

The authors of several retrospective studies[35-37] in patients with NSCLC have reported that the SUV of the primary tumor at the time of diagnosis is predictive of disease control and survival. A relationship has been observed between SUV and other important predictive factors, such as staging, tumor size, and clinical situation. Sasaki et al[38] demonstrated that the SUV of the primary tumor was the strongest prognostic factor in patients who underwent curative surgery or radiotherapy. An SUV under 5.0 was associated with a longer disease-free interval and a higher overall survival rate than one over 5.0. In a recent study of 397 patients, Bryant and colleagues[39] found the SUV of mediastinal lymph nodes to be a predictor of malignancy, and when a cutoff point of 5.3 was used accuracy increased to 92% for each N2 nodal station.

Radiation Therapy Planning

Accurate tumor staging facilitates the planning of therapies used to treat cancer patients. FDG-PET is very useful for diagnosing malignant lesions and gives better results than either CT or MRI in many kinds of tumors. The integration of the metabolic information from PET and the anatomic data from CT increases diagnostic yield in the delineation of lesions in 20% to 30% of patients.

Integrated PET-CT scanners play a key role in radiation therapy planning in the calculation of both the radiation

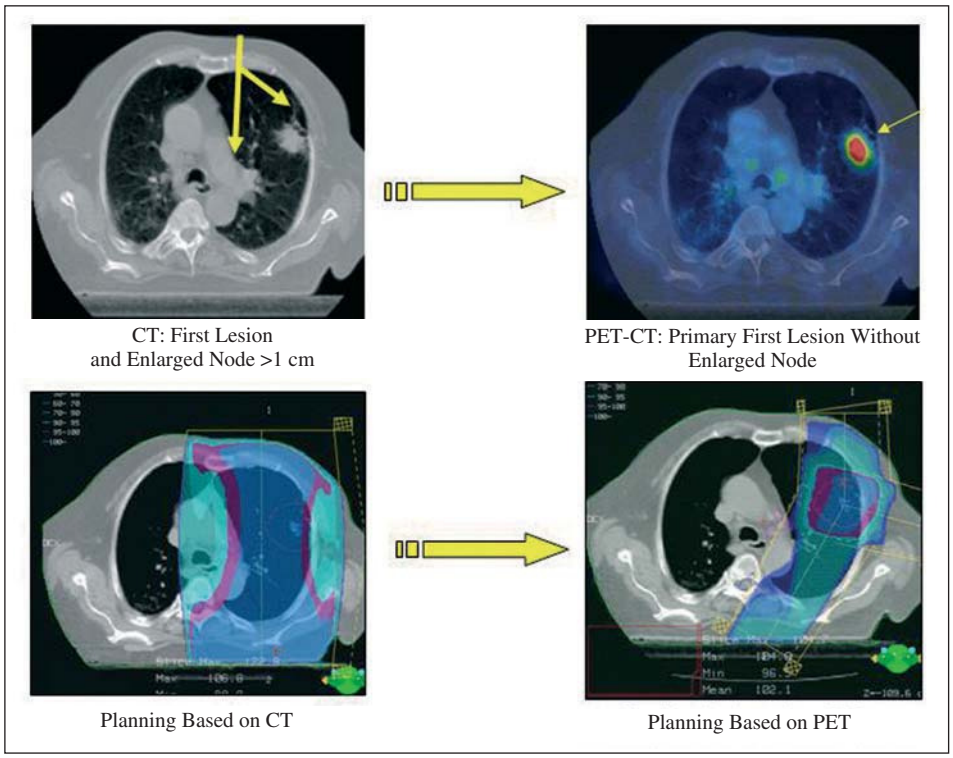

Figure 6. Radiation therapy planning based on positron emission tomography (PET). Reduction in target tumor volume. CT indicates computed tomography.

dose and the volume of the target tumor; this influence has been demonstrated in studies in which these 2 techniques were performed separately.[40-43] FDG imaging can perfectly delineate the areas of malignancy and their intensity inside the anatomic image of the tumor. This leads to more effective treatment and minimizes damage to healthy tissue around the tumor. Recent studies show that the metabolic information supplied by PET imaging can alter the radiation treatment volume in up to 56% of cases (Figure 6).[44,45] Another recent addition to the field of radiotherapy planning is the introduction of a new parameter: biological tumor volume.

Basing radiation therapy planning on information provided by integrated PET-CT scans facilitates correct classification of lesions that cannot be conclusively identified using CT alone because of similarity in densities. Moreover, it can also detect previously unobserved distant lesions owing to the high sensitivity of FDG imaging in the detection of malignant disease.

The use of hybrid PET-CT scanners for planning 3-dimensional radiation therapy allows more precise volume delineation than CT alone. Integrated scanning also reduces the risk of error in the topographic localization of lesions and minimizes the dose of ionizing radiation received by non-target structures. It transforms current concepts of radiation therapy planning by incorporating metabolic and biological aspects of neoplastic disease rather than restricting the process solely to anatomic information. In the not too distant future, the association of new modalities, such as tomotherapy, with PET-CT imaging (4-dimensional) will result in a substantial improvement in both local disease control and the development of complications following radiation treatment.

Detection of Malignant Pleural Disease

In the case of malignant pleural mesothelioma, surgical treatment is possible in the initial stages of the disease while patients with more advanced disease require treatment with a variety of therapeutic measures (chemotherapy, radiotherapy, and surgery). Meignan et al[46] reported FDG-PET to be useful for detecting node involvement and distant metastases in the early stages of mesothelioma (as in Figure 7) while indicating that the principal drawback of the technique was the difficulty of detecting the small diffuse lesions that occur frequently in this disease. These authors concluded that SUVs above 4 were a predictor of mortality and that FDG metabolism could be used as a predictor of response to chemotherapy.

PET-CT can improve staging of malignant pleural mesothelioma as compared to other imaging techniques.[47] Using PET-CT imaging, Erasmus et al,[48] detected lesions precluding surgery in 37.9% of cases and unexpected extrathoracic metastases in 24.1% when they studied 29 patients judged after clinical and conventional radiologic evaluation to be suitable candidates for extrapleural pneumonectomy. In a recent publication comparing PET-CT with CT alone in 15 patients, Ambrosini et al[49] reported that PET-CT did not provide any additional information on the primary tumor but it did detect unexpected mediastinal node involvement in 40% of patients and

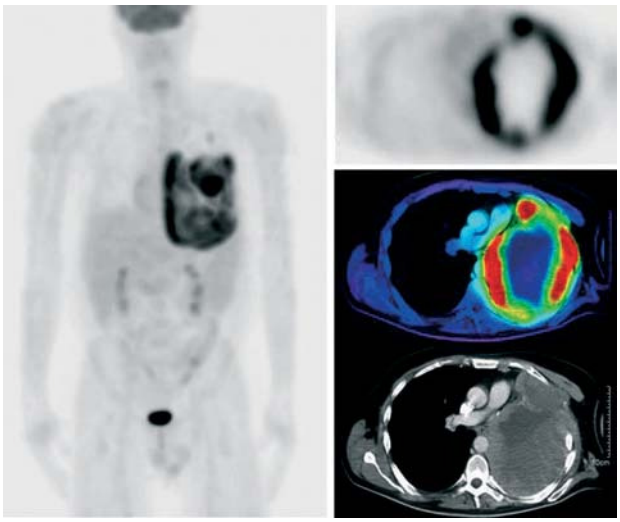

Figure 7. Detection of active lesions in a malignant pleural mesothelioma. No evidence of extrathoracic involvement.

distant metastases in 20%. In that study, PET-CT results led to changes in therapeutic management in 33.3% of patients. Other authors have published similar results on the yield of PET-CT in this clinical situation.[50]

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